REMARKS

Claims 1-76 are pending in the case. Claims 1-3, 8, 9, 11-13, 17-19, 21, 24-27, 30-34, 36-42, 66-68, 75-76 are under examination. Claims 4-7, 10, 14-16, 20, 22, 23, 28, 29, 35, 43-65, and 69-74 are withdrawn from consideration for being drawn to a non-elected invention. Claims 1, 17 and 30 have been amended. The amendments to claims 1, 17, and 30 are supported for example in claims 3 and 32. Claims 77-83 have been added. The claims are supported throughout the specification. For example, claims 77-80 are supported, for example, on page 14, lines 15-26 and in Examples 13-16. Claims 81 to 83 are supported, for example, on page 7, lines 4-7 and in Example 14. The amendment includes no new matter.

Rejections under 35 U.S.C. § 112, first paragraph, Written Description

Claims 1-3, 8, 11-13, 17-19, 21, 24-27, 30-33, 36-42, and 66-68 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The rejected claims are directed to i) methods for modulating endothelial cell (EC) proliferation in a mammal by increasing or decreasing ezrin activity (claims 1-3, 8, 11-13, and 66-68); ii) methods for inducing formation of new blood vessels in a mammal by decreasing ezrin activity (claims 17-19, 21, 24-27, and 66-68); or iii) methods for reducing the severity of blood vessel damage in a mammal by decreasing ezrin activity (claims 30-33, 36-42, and 66-68). In support of the rejection for failing to comply with the written description requirement, the Office alleges that Applicants have not provided evidence of possession of a compound that will decrease ezrin activity by providing sufficient distinguishing identifying characteristics of the genus. For the reasons detailed below, Applicants respectfully disagree with the rejection and request that it be withdrawn.

The Office Action extensively cites MPEP 2163 regarding what is required for characteristics that can provide evidence that the Applicant was in possession of the invention. The portion of the paragraph referring to *University of Rochester v. G.D.Searle & Co.* (citation omitted, hereinafter *Rochester*) is in bold. In *Rochester*, "the patent did not disclose any compounds that can be used in the claimed methods." The Office Action states that "the instant claims are drawn to methods of treatment with compounds with no disclosed structures whatsoever." The Office Action then notes that, in fact, one compound is claimed, Y27632,

which is enabled. Applicant respectfully disagree. The only claimed compound in the claims under examination is Y27632. The claims recite many other compounds, supported by the specification, that are not under examination, but are dependent on the generic claim. Election of a species does not remove support for the broad claim.

The situation in *Rochester* was entirely different from the instant claims. In *Rochester*, a new gene and protein had been discovered. No known agonists or antagonist of the protein were known. In the instant case, the claims are drawn to modulation of a known protein. It is noted that US Patent 6,399,584 (cited page 17, line 25) claims a peptide that has the same activity as a dominant negative ezrin protein (withdrawn claims 10, 20, and 35). TNF antagonists and antibodies directed to TNF were known at the time of the instant application (withdrawn claim 6) as noted on page 16, lines 17-19 and page 17, lines 9-19. On page 17, lines 1-7, the specification teaches that Rho kinase inhibitors were known and that Y27632 is simply a preferred inhibitor. Further examples provided in the specification will not be recited here. Applicant submits that the specification, and withdrawn claims, provide sufficient written description for agents that can modulate the activity of ezrin.

Moreover, the claims are drawn to a method, not a composition. The invention includes the realization of the role of ezrin in mediating proliferation of endothelial cells, particularly in repose to TNF-α which is frequently produced as a result of blood vessel damage and ischemia. Having realized the interaction of ezrin with TNF-α, cyclin A, Rho, and Rho kinase, one skilled in the art could select an agent to manipulate the activation or expression ezrin or its interacting proteins to modulate signaling through the pathway. As the proteins in the pathway were all known at the time of filing, inhibitors and activators of the compounds were known and their methods of use were understood by those of skill in the art. Having disclosed the pathway in the instant application, one of skill in the art would know how to practice the invention with any of a number of agents that would modulate signaling through the pathway.

The test for sufficiency of support under the written description requirement was provided by the Court in *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991), which stated, "Although [the applicant] does not have to describe exactly the subject matter claimed…the description must clearly allow persons of ordinary skill in the art to

recognize that [he or she] invented what is claimed" (citations omitted). In the instant application, what is claimed are methods of modulating endothelial cell proliferation by modulating ezrin activity, methods of inducing new blood vessel formation by decreasing ezrin activity, and methods of reducing the severity of blood vessel damage by decreasing ezrin activity. The claimed methods require modulating ezrin activity in a mammal by administering an ezrin modulating agent. Contrary to what is instantly claimed, the Office Action appears to present written description arguments as though the claims were directed to compositions. Applicant notes that the application includes working examples of modulation of ezrin activity using the Y27632 and a dominant negative ezrin.

The application provides examples of structures as well as methods to test compounds that can act to modulate ezrin activity. Applicants respectfully submit the written description requirement does not necessitate an encyclopedic recounting of all known and yet to be discovered compounds, including variants and alternate isoforms, that might be used in the claimed methods when a generic description is provided. To hold Applicants claimed methods to this kind of standard is inappropriate and deprives Applicants of protection for the full scope of the claimed invention. Furthermore, Applicants have provided not just a generic description, but have provided data using two different ezrin modulating agents and have provided citations for patent and non-patent literature that teaches compounds that fall within the classes of compounds in the pending and withdrawn claims. One of ordinary skill in the art, armed with the specification, would not only be able to practice the methods as currently claimed, but would also recognize Applicants to be in possession of the invention as instantly claimed at the time the application was filed.

Applicants' arguments are strongly supported by Federal Circuit decisions. For example, *In Union Oil Co. v. Atlantic Richfield Co.* 208 F.3d 989, 997 (Fed. Cir. 2000), the court concluded, "A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language." In accordance with this conclusion, Applicants provide explicit examples of numerous ezrin modulating compounds targeting two different proteins in the ezrin signaling pathway. Applicants are NOT required to explicitly describe each and every known or yet to be discovered compound that may be of used in the claimed methods.

In addition, the initial burden of proof in establishing whether the claims are supported by an adequate written description falls upon the Examiner, "The description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption" (MPEP 2163.04 and *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)). Furthermore, the Examiner "must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of the evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims (*In re Wertheim*, 541 F.2d at 263, 191 USPQ at 97 (CCPA 1976)). The Examiner has not provided sufficient evidence to show that one of skill in the art would not recognize Applicants to be in possession of the full scope of the methods claimed.

Applicants respectfully submit the subject matter of the instantly claimed methods was more than adequately described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors were in possession of the claimed invention at the time the application was filed. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph for a lack of written description.

Rejections under 35 U.S.C. § 112, first paragraph, Enablement

Claims 1-3, 8, 9, 11-13, 17-19, 21, 24-27, 30-34, 36-42, 66-68, 75-76 are rejected under 35 U.S.C. §112 as failing to comply with the enablement requirement. The Office Action alleges that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Applicant respectfully disagrees.

The Office Action points to Shibata to demonstrate the action of the Rho kinase inhibitor Y27632 in preventing neointimal lesion formation and that the inhibitor is proposed to work by promoting SMC apoptosis. Applicant notes that neointimal lesion formation is not angiogenesis and is never desirable. Although both processes require the migration of muscle cells, the processes are not the same.

The Office Action suggests that other compensatory mechanisms may occur upon administration of an ezrin inhibitor that could negate the effects of inhibition of Rho kinase. Applicant submits that such an argument is not relevant to the claims. It is well known that therapeutic agents are frequently given as cocktails of a combination of agents or different agents are administered sequentially for treatment. The claims do not require that the ezrin modulating agents be able to act independently and indefinitely to produce the desired outcome.

Applicants have included claims to contacting the endothelial cells ex vivo with the ezrin modulating agents and to local administration of the ezrin modulating agents. Methods of local delivery of unelected nucleic acid based ezrin modulating agents can be performed, for example, using the methods taught and claimed in US Patent 5,652,225. Alternatively, the ezrin modulating agent could be delivered for a short time, e.g., when TNF-α levels are elevated, as opposed to Shibata which states that some of the effects seen in the study may be due to long term administration of the compound. Methods of dosing and monitoring a subject for response to a therapeutic agent are well within the skill in the art. Shibata notes the problems inherent in their experimental methods. In treating a subject, one is not bound to a predetermined protocol. Therefore, many of the problems could be avoided.

The Office Action also points to Van Nieuw Amerongen to demonstrate the activity of Rho kinase inhibitors *in vitro* and their activity in conjunction with VEGF in cell migration. As taught in the instant application, ezrin acts to inhibit the action of TNF-α which inhibits endothelial cell growth after injury which is nearly always accompanied by inflammation. "Wounding" of a culture in vitro does not result in an inflammatory response, e.g., no TNF-α would be released. Moreover, Van Nieuw Amerongen is interested in migration, not proliferation, as claimed in the instant invention in independent claims 1 and 17, as angiogenesis requires proliferation as well as migration. As noted above, wounding *in vivo* is substantially different from "wounding" *in vitro*. Van Nieuw Amerongen teaches only wounding *in vitro*.

The Office Action states that "from the instant disclosure, one skilled in the art would expect that decreasing ezrin activity should reduce the severity of blood vessel damage when a mammal exposed to conditions conducive to damaging blood vessels." Again, considering *Cross v. Iizuka* (citation omitted), a reasonable correlation is provided between the ***in vivo***

ischemia model in the specification in Example 14. Applicant submits that a mouse does present a "complex biological system." In the mouse, vasculature was damaged. When the ezrin modulating agent was administered to the mouse, blood flow recovery was improved relative to a control animal. In the "complex biological system", angiogenesis occurred, despite suggestions of other references that angiogenesis might be inhibited by inhibition of Rho kinase. Having demonstrated *in vitro* the functional equivalence of a number of ezrin modulating agents in endothelial cells, one skilled in the art would expect that at least a portion of ezrin modulating agents, of which there are many, would act in the same manner. Example 14 provides a routine and appropriate model, as demonstrated by the reference to 10 patents or applications that provide further details on the method, for testing ezrin modulating agents for activity in a "complex biological system". Applicant submits that the invention is fully enabled. Withdrawal of the rejection is respectfully requested.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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